

WHAT IS CLAIMED IS:

1. A method for making a stabilized protein or fragment thereof comprising:
 - (a) selecting one or more residue pairs in a polypeptide chain or chains
for cross-linking using one or more statistical criteria; and
 - (b) cross-linking the residue pairs.

5

10

2. The method of claim 1, wherein the stabilized protein or fragment is selected from the group consisting of a hormone, a receptor, a growth factor, an enzyme and an antibody.

3. The method of claim 2, wherein the enzyme is a lipase or the antibody fragment is an Fv fragment.

15

4. The method of claim 1, wherein the one or more statistical criteria used for selection of residue pairs in step (a) are selected from the group consisting of statistical filter one through statistical filter six.

20

5. The method of claim 1, wherein tyrosine residues are cross-linked.

6. The method of claim 6, wherein cross-linking is catalyzed by a catalyst selected from the group consisting of polyhistidine, Gly-Gly-His and metalloporphyrin.

25

7. The method of claim 6, wherein the cross-linked tyrosine residues are introduced into the stabilized protein complex prior to cross-linking by recombinant nucleic acid methods.

30

8. A method for identifying a residue pair in a polypeptide chain or chains that, following substitution with tyrosine and cross-linking, is least likely to be disruptive of overall protein structure, comprising applying one or more statistical criteria selected from the group consisting of statistical filter one through statistical filter six.

9. A protein cross-linked by the method of claim 1.

35

10. A protein comprising at least one di-tyrosine cross-link, which protein retains at least one function displayed by the protein in the absence of di-tyrosine cross-linking.

11. The protein of claim 10, further comprising at least one amino acid which was substituted for a tyrosine residue such that the residue substituted for the tyrosine residue is not cross-linked under cross-linking conditions.

12. The protein of claim 10, wherein the function retained is selected from the group consisting of catalytic activity and binding specificity.

13. The protein of claim 10 which is selected from the group consisting of an enzyme and an antibody or fragment thereof.

14. A pharmaceutical composition comprising the protein of any one of claims 9 to 13.

15. The pharmaceutical composition of claim 14, further comprising a pharmaceutically acceptable carrier.

16. The pharmaceutical composition of claim 14 which is suitable for *in vivo* use in humans.

17. A kit comprising in one or more containers the protein of any one of claims 9 to 13.

18. A method for making a stabilized protein comprising:

- (a) selecting one or more residue pairs in a polypeptide chain or chains for cross-linking, wherein the selected residues are tyrosine when cross-linked; and
- (b) cross-linking the residue pairs.

19. The method of claim 18, wherein the cross-link reaction occurs in the presence of an oxidant selected from the group consisting of hydrogen peroxide, oxone,

magnesium monoperoxiphthalic acid hexahydrate (MMPP), a photogenerated oxidant, and ammonium persulfate.

20. The method of claim 19, wherein cross-linking is catalyzed by a catalyst
5 selected from the group consisting of polyhistidine, Gly-Gly-His and metalloporphyrin.

10

15

20

25

30

35